

Supplementary file

Table S1. Covariates for adjusted model

Covariates	ATC codes	Name
Anticoagulants	B01AA	Vitamin K antagonists
	B01AB	Heparin
	B01AE	Direct thrombin inhibitors
	B01AF	Direct factor Xa inhibitors
	B01AX05	Fondaparinux
Antiplatelet drugs	B01AC	Platelet aggregation inhibitors excl. heparin
Prothrombotic drugs	G03AA, G03AB	Hormonal contraceptives (progestogens and estrogens)
	G03C	Estrogens
	G03F	Progestogens and estrogens in combination in the treatment of menopausal symptoms
	G03H	Antiandrogens
	G03XA	Danazol
	G03XC	Selective estrogen receptor modulators
	L04AX04	Lenalidomide
	L04AX02	Thalidomide
	B03X	Other antianemic preparations (epoetin)
	N05A (N05AN excluded)	Antipsychotics
	M05BX03	Strontium ranelate
	L04AA10	Sirolimus
	L04AA18	Everolimus
	H01BA02	Desmopressin
	H02AB	Glucocorticoids
	M01A	Non-steroidal anti-inflammatory drugs
	B02BX05	Eltrombopag
	J06B	Immunoglobulins
	R03DX05	Omalizumab
	B02AA02	Tranexamic acid
Vasoconstrictive drugs	R01B	Nasal decongestants for systemic use
	R01AA, R01AB	Nasal decongestants for topical use, sympathomimetics
	N02CC	Antimigraine preparations with selective serotonin (5HT1) agonists
	N02CA	Antimigraine preparations with ergot alkaloids
	N04BC01, G02CB01	Bromocriptine
	G02CB02	Lisuride
	G02CB03	Cabergoline
	G02AB01	Methylergometrine
	C01CA17	Midodrine

Table S2. Results of the main and stratified analyses. Crude and adjusted ORs for overall ADA use, and stratified by type of ADA, sex, age, and dementia status. Figures are number of individuals unless stated otherwise

	Individuals	ADA use		OR (95% CI)	
		Risk period	Reference period ^a	Crude	Adjusted
Sex					
Male					
CCO cases	885	451	334	4.12 (3.57-4.76)	4.13 (3.57-4.78)
CCO controls	7,063	1,663	4,240	1.16 (1.09-1.22)	1.15 (1.09-1.22)
CTC ratio				3.57 (3.06-4.16)	3.59 (3.06-4.20)
Female					
CCO cases	1,727	799	726	3.35 (3.02-3.71)	3.29 (2.97-3.66)
CCO controls	14,796	3,465	8,925	1.13 (1.09-1.18)	1.13 (1.09-1.18)
CTC ratio				3.29 (2.97-3.66)	2.91 (2.60-3.26)
Age, years					
<70					
CCO cases	993	470	392	3.63 (3.16-4.14)	3.47 (3.02-3.98)
CCO controls	9,184	2,048	5,545	1.09 (1.03-1.14)	1.09 (1.03-1.15)
CTC ratio				3.33 (2.88-3.85)	3.19 (2.75-3.70)
≥70					
CCO cases	1,619	780	668	3.58 (3.55-3.98)	3.58 (3.22-3.99)
CCO controls	12,675	3,080	7,620	1.17 (1.13-1.23)	1.17 (1.13-1.23)
CTC ratio				3.05 (2.72-3.41)	3.05 (2.72-3.43)
Dementia					
Yes					
CCO cases	157	67	75	2.68 (1.91-3.74)	2.65 (1.88-3.72)
CCO controls	901	204	566	1.02 (0.87-1.21)	1.03 (0.87-1.22)
CTC ratio				2.61 (1.80-3.80)	2.24 (1.58-3.18)
No					
CCO cases	2,455	1,183	985	3.67 (3.36-4.00)	3.62 (3.32-3.96)
CCO controls	20,958	4,924	12,599	1.14 (1.11-1.18)	1.14 (1.11-1.18)
CTC ratio				3.21 (2.92-3.52)	3.17 (2.89-3.48)

Abbreviations: CCO Case-crossover; CTC Case-time-control; OR Odds ratio; CI Confidence interval

^a Individuals exposed in at least one reference period

Adjusted OR: values of OR were adjusted for prothrombotic or vasoconstrictive drugs, anticoagulants and antiplatelet drugs

Table S3. Results of the sensitivity analyses. Crude and adjusted ORs for different risk periods, and including individuals with a history of hospitalization during the observation period. Figures are number of individuals unless stated otherwise

	Individuals	ADA use		OR (95% CI)	
		Risk period	Reference period ^a	Crude	Adjusted
7-day risk period ^b					
CCO cases	2,138	923	546	5.16 (4.64-5.75)	5.10 (4.57-5.70)
CCO controls	17,217	2,721	7,447	1.08 (1.04-1.13)	1.10 (1.05-1.15)
CTC ratio				4.76 (4.24-5.35)	4.66 (4.14-5.25)
21-day risk period ^c					
CCO cases	2,612	1,470	1,060	2.87 (2.65-3.12)	2.83 (2.61-3.08)
CCO controls	21,859	7,326	13,165	1.09 (1.06-1.12)	1.10 (1.06-1.13)
CTC ratio				2.64 (2.42-2.87)	2.59 (2.37-2.82)
Hospitalization in the 70-day period before stroke ^d					
CCO cases	3,407	1,572	1,401	3.40 (3.16-3.66)	3.38 (3.13-3.64)
CCO controls	27,370	6,293	16,488	1.12 (1.08-1.15)	1.12 (1.08-1.15)
CTC ratio				3.05 (2.82-3.30)	2.02 (2.79-3.28)

Abbreviations: CCO Case-crossover; CTC Case-time-control; OR Odds ratio; CI Confidence interval

^a Individuals exposed in at least one reference period

^b Observation period: 49 days before stroke. Risk period: days [-7, -1]. Three matched reference periods: days [-49, -43], [-42, -36], and [-35, -29]

^c Observation period: 70 days before stroke. Risk period: days [-21, -1]. Two matched reference periods: days [-70, -50], and [-49, -29]

^d Risk period: days [-14, -1]. Three matched reference periods: days [-70, -57], [-56, -43], and [-42, -29]

Adjusted OR: values of OR were adjusted for prothrombotic or vasoconstrictive drugs, anticoagulants and antiplatelet drugs

Table S4. Results of the main and sensitivity analyses. Crude and adjusted ORs for different risk periods. Figures are number of individuals unless stated otherwise.

	Individuals	ADA use		OR (95% CI)	
		Risk period	Reference period ^a	Crude	Adjusted
Main analysis					
Risk period [-14, -1] ^b					
CCO cases	2,612	1,250	1,060	3.59 (3.31-3.91)	3.55 (3.26-3.87)
CCO controls	21,859	5,128	13,165	1.14 (1.10-1.18)	1.14 (1.10-1.18)
CTC ratio				3.16 (2.89-3.46)	3.12 (2.85-3.42)
Sensitivity analyses					
Risk period [-14, -3] ^c					
CCO cases	2,136	850	960	2.68 (2.44-2.95)	2.68 (2.44-2.95)
CCO controls	17,717	4,024	10,260	1.15 (1.11-1.20)	1.16 (1.11-1.20)
CTC ratio				2.33 (2.10-2.57)	2.32 (2.09-2.57)
Risk period [-14, -7] ^d					
CCO cases	1,459	429	661	1.95 (1.72-2.02)	1.96 (1.73-2.22)
CCO controls	11,611	2,306	6,074	1.12 (1.07-1.18)	1.12 (1.07-1.18)
CTC ratio				1.73 (1.52-1.98)	1.75 (1.53-2.00)

Abbreviations: CCO Case-crossover; CI Confidence interval; CTC Case-time-control; OR Odds ratio

^a Individuals exposed in at least one reference period

^b Observation period: 70 days before stroke. Risk period: days [-14, -1]. Three matched reference periods: days [-70, -57], [-56, -43], and [-42, -29]

^c Observation period: 64 days before stroke. Risk period: days [-14, -3]. Three matched reference periods: days [-64, -53], [-52, -41], and [-40, -29]

^d Observation period: 52 days before stroke. Risk period: days [-14, -7]. Three matched reference periods: days [-52, -45], [-44, -37], and [-36, -29]

Adjusted OR: values of OR were adjusted for prothrombotic or vasoconstrictive drugs, anticoagulants and antiplatelet drugs

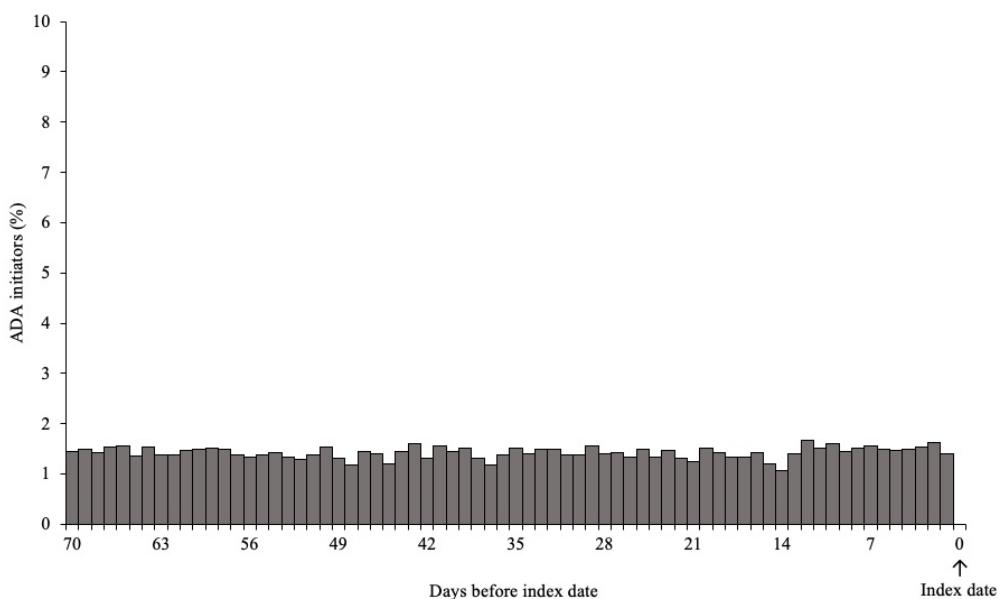


Figure S1. Distribution of ADA initiation over the 70 days before index date among time-trend controls

ADA initiators (%): number of cases who initiated ADA a given day in the 70-day period before index date related to total number of time-trend controls (n=21,859). Total of histogram grey bars equals 100%.